Whitepaper : Defining and investigating cognitive reserve, brain reserve, and brain maintenance

Reserve Resilience Protective Fact

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Review Article

Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance

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Abstract Several concepts, which in the aggregate get might be used to account for "resilience" against age- and disease-related changes, have been the subject of much research. These include brain reserve, cognitive reserve, and brain maintenance. However, different investigators have use these terms in different ways, and there has never been an attempt to arrive at consensus on the definition of these concepts. Furthermore, there has been confusion regarding the measurement of these constructs and the appropriate ways to apply them to research. Therefore the reserve, resilience, and protective factors professional interest area, established under the auspices of the Alzheimer's Association, established a whitepaper workgroup to develop consensus definitions for cognitive reserve, brain reserve, and brain maintenance. The workgroup also evaluated measures that have been used to implement these concepts in research settings and developed guidelines for research that explores or utilizes these concepts. The workgroup hopes that this whitepaper will form a reference point for researchers

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in this area and facilitate research by supplying a common language.

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1. Reserve

The study of what makes people with certain life histories resilient against aging or disease is important because it has implications for policy and intervention; however, there are likely several complex and highly interactive mechanisms that lead to these individual differences in vulnerability to decline.

Reserve is a heuristic to help explain individual differences in cognition, function, or clinical status relative to aging and brain disease. There are many potential mechanisms implicated in this complex construct, probably reliant on both structural and functional brain mechanisms. Resilience is a more general term referring to multiple reserve-related processes. Therefore, the proposed nomenclature focuses on definitions and measures of cognitive reserve (CR), brain reserve (BR), and brain maintenance (BM), as well as expectations for research derived from those concepts.

Definitions of CR, BR, and BM are evolving, as are the ways in which these constructs are best studied. As such, the ideas presented here are offered as a conceptual framework that will propagate in defining, measuring, and studying reserve. In addition, this paper is written in the context of cognitive aging and brain pathologies such as Alzheimer's disease (AD). Further work may be needed to ensure that these definitions apply well across other conditions that affect brain functioning.

2. Cognitive reserve

2.1. Definition of CR

The term CR refers to the adaptability (i.e., efficiency, capacity, flexibility [For tentative definitions of these concepts, refer to the section on functional imaging approaches to measuring CR.]) of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult. At the brain level of analysis, CR is proposed to be supported by more adaptable functional brain processes. Functional brain processes refer to the networks of brain regions associated with performing a task and the pattern of interactions between these networks.

Differences in CR are accordingly determined by individual differences in these existing cognitive or functional brain processes. These processes can be influenced by the interaction of innate (e.g., in utero, or genetically determined) individual differences and lifetime exposures. CR is therefore not fixed or immutable. Relevant lifetime exposures include, but are not limited to, early-life general cognitive ability (e.g., intelligence), education, occupation, physical exercise, leisure activities, or social engagement.

CR is an active model of reserve, meaning that dynamic cognitive and underlying functional brain processes cope with brain changes or damage. This does not connote that these cognitive processes must be invoked intentionally. When age- or disease-related brain changes occur, individual differences in the cognitive processes can influence how successfully a person can cope with these changes. The cognitive/functional brain processes that support CR may already be present before the onset of brain pathologies. Alternately, when challenged with age- or disease-related brain changes, there may be individual differences in the need or ability to adapt new, or compensatory cognitive/functional processes to maintain function.

2.2. Measures of CR

As a theoretical construct, CR has rarely been assessed *directly*. The closest direct measure of CR may stem from characterization and measurement of functional brain processes, but even those studies do not necessarily directly measure CR because they are typically embedded in a particular methodology and set of conditions as mentioned below. Rather, studies often rely on the following three broad methods to quantify and measure CR.

2.2.1. Sociobehavioral proxies of CR

From the outset, researchers have relied on "convenience proxies," sociobehavioral indices assumed to covary with and indeed contribute to the development of CR. These include education, IQ, occupational complexity, leisure and physical activity, and other protective factors that have been identified, most often in epidemiologic research. Clearly, such factors are global in nature and do not imply any specific functional mechanisms. Rather, they are *formative*, meaning that they attempt to represent those experiences that contribute to the development of CR.

Accordingly, proxies must be used cautiously and not be treated as direct measures of CR. Rather, they must always be considered in the context in which they were originally discovered, that is, the degree to which they might account for individual differences in the relationship between the underlying brain state and level of function. As a case in point, the observation that educational attainment is associated with reduced age-specific risk of developing Alzheimer's dementia could suggest that individuals with higher education can "cope with" greater severity of AD-related brain changes before becoming demented. When in vivo biomarker imaging or postmortem data confirm greater severity of Alzheimer's pathology along with relatively

preserved functioning for individuals with higher education, this interpretation about CR is more justifiable.

Recent advances in molecular genetics have enabled the calculation of polygenic risk scores for CR proxies such as educational attainment and general cognitive ability. This may provide an alternate approach for estimating some CR proxy scores.

Because CR is dynamic and influenced by different exposures across the lifespan, it is likely that each of its component lifestyle proxy factors could contribute uniquely to CR. Some researchers have studied individual factors in isolation, in permutation, or synthesized into a summary measure. Summary proxies for CR need to take care not to simply identify shared variance among purported protective factors, as this could fail to capture the unique contributions of individual exposures. Also, such commonalities might be related to factors other than reserve. Still, summary CR measures could be useful in clinical or research situations.

When there is evidence for a CR proxy, further understanding of whether the proxy is a causal factor or reflective of reverse causation is important. For example, engagement in cognitive activities might contribute to CR and be associated with reduced risk of dementia, but it is also possible that people reduce these activities in the prodromal phase of dementia and therefore appear to have lower CR. These determinations are made more complex with summary proxies because the constituent elements may not operate in the same way.

2.2.2. Residual approaches to quantify CR

Recently, several investigators have used a "residual" approach to measuring CR. This approach models demographic and brain predictors of cognition and treats the variance in cognition that is not explained by these predictors as a measure of current CR. The validity of this approach is dependent on the specification of the predictors and outcome measure in the model. Brain measures that are used to predict cognition may only partially capture underlying brain physiology and pathology. The residual approach may share limitations of the composite approach using observed lifestyle variables described previously: when defining CR by that, which is *not* explained by known brain predictors, there is a high risk of including many things other than reserve. Also, the use of this approach will necessarily differ from study to study, depending on what set of predictor and outcome variables are used, and introduce variability across studies. On the other hand, this approach has advantages: it is a more direct measure of CR, and it is potentially dynamic, changing as CR is built up or depleted. The residual approach to CR may therefore be more informative at the individual level. Thus, this approach is worthy of further exploration.

2.2.3. Functional imaging approaches to measuring CR

Various functional imaging approaches have been used to try to capture the "neural implementation" of CR. One goal is to identify resting state or task-related functional activation brain networks that may underlie CR in that their expression (1) is associated with typical reserve sociobehavioral proxies and (2) moderates the effect of brain changes on cognition. If such networks are identified and validated, their degree of expression in any individual may be a more direct measure of CR than other types of proxies. A challenging issue here is that activation networks may be specific to given tasks and also dependent on the specific brain regions that are or are not affected. Identification of CR networks that are active across multiple tasks or generic resting networks may be productive in this setting. Such generic networks still may not provide a complete explanation for CR. For instance, it is possible that CR is subserved through neuronal processing mechanisms that cut across functional imaging designs such as more flexible connections, or greater dynamic range or responsivity. For these questions, other modalities for studying the brain may be indicated. There is also a clear need for a conceptual counterpart to this idea at the neurobiological levels of molecules, cells, and systems.

3. Brain reserve

3.1. Definitions of BR

Brain reserve is commonly conceived as neurobiological capital (numbers of neurons, synapses, etc.). BR implies that individual variation in the structural characteristics of the brain allows some people to better cope with brain aging and pathology than others before clinical or cognitive changes emerge. At any point in time, BR is a fixed construct (i.e., the neurobiological capital available at that time), but see the definition of BM below for how life experience can potentially add to BR.

Cognitive or functional deficits would only occur after a certain fixed threshold has been reached, and in those with greater BR, there would simply be "more to lose" before cognitive or functional impairment emerges. BR can therefore be considered a more *passive* form of reserve in that it does not invoke active adaptation of functional or cognitive processes in the presence of insult as does CR.

Despite the explicit reference to neurobiological substrate, there is a need for identification of corresponding concepts in neurobiology and for models at the level of cells and molecules. So far, BR refers to a rather macroscopic construct that is not linked to identifiable neurobiological causes or mechanisms of finer granularity.

Colloquially, BR might be considered the "hardware," whereas CR would be the "software." This distinction is convenient, but not completely accurate, because cognition must have a biological basis. In other words, even the CR "software" must rely on underlying cellular/molecular mechanisms. Because of the blurred distinction, the term "wetware" (referring to the amalgamated interaction of hardware and software) has occasionally been used to describe

this particular relationship in the brain. Still, at this point, it is not possible to map CR (or any cognitive process) onto defined biological phenomena in a one-to-one, straightforward, or even linear way. Thus, the current definitions of CR and BR are made at qualitatively different levels. These distinctions may be replaced in the future as our knowledge progresses. Integration with concepts at the cellular and molecular level will be necessary, and the integration will call for systems neuroscience approaches that transcend traditional boundaries of research domains and disciplines.

Another reason for an operational distinction between BR and CR is that the two account for unique portions of the variance in clinical or cognitive status. The distinction is also conceptually important because CR is an active, dynamic process, whereas BR is passive. Finally, it is useful to distinguish between BR and CR because they tend to map onto different techniques used in our neuroimaging research; that is, structural and functional methods, respectively.

3.2. Measures of BR

Theoretically, BR encompasses all the anatomical or structural aspects of the brain that could be measured using *in vivo* or *postmortem* techniques, but exclusive of neuropathology such as AD plaques and tangles, and infarcts, because BR is hypothesized to be protective against these. In practice, this differentiation is challenging because pathology and BR can be expressed in the same brain areas.

Historically, researchers have also used proxies to estimate this BR, including gross whole-brain measures reflective of *peak* or *premorbid* brain volume, including intracranial volume, or even head circumference. More recently, researchers have begun to incorporate more fine-grained measures such as specific patterns of gray matter volume, cortical surface area, cortical thickness, PET measures of synaptic integrity, or white matter microstructural properties. However, these approaches need to carefully distinguish between those structural characteristics totemic to BR as opposed to those simply reflective of neuropathologic volume loss secondary to insult (e.g., atrophy secondary to stroke, AD). A further complication is that some of these brain markers (e.g., cortical thickness or brain volume) might reflect a combination of BR and BM when measured longitudinally in older adults (see below).

4. Brain maintenance

4.1. Definitions of BM

While BR refers to the neurobiological capital at any point in time, BM is defined as reduced development over time of age-related brain changes and pathology based on genetics or lifestyle. BM also reflects the fundamental notion that the brain is modifiable based on experience. Genetics and lifestyle, including many of the same life exposures associated with differential CR, can impact BM. This can lead to individual differences in morphologic brain decline associated with normal aging. Lifestyle features may also be associated with differences in pathologic features such as stroke or microvascular brain changes; whether they could influence the aggregation of pathology such as amyloid plaques or tau tangles is an ongoing research question. This would be a fundamental distinction between BM and BR; BR, as noted previously, does not protect against the accumulation of brain pathology, but it does protect against the effects of the pathology itself.

BR and BM are fundamentally related concepts. It remains an open question as to whether in fact they are the same concept viewed at different timescales. By definition BM represents the process of maintaining, or perhaps enhancing, the brain, whereas BR represents the status of the brain at a point in time. BM refers to the reduction of the impact of primary pathology (e.g., age-related brain changes) on brain integrity. Better BM could thus sustain higher BR.

4.2. Measures of BM

Brain maintenance is best measured longitudinally, by demonstrating relative preservation of brain morphology. An alternate is a residual approach, where, for example, an individual's current brain status is compared with the state typically expected at that age. Further longitudinal studies should consider sociobehavioral CR proxies that change with time, such as cognitive and leisure activities, as well as traditional BR proxies to further refine putative measures of BM.

5. Research considerations

5.1. Cognitive reserve

Research aimed at further elucidating CR requires the inclusion of three components—the status of the brain (reflecting brain change or pathology), clinical or cognitive performance outcomes, and a measure of reserve: either a sociobehavioral proxy (i.e., an index of lifetime exposure/premorbid ability) or a functional brain measure.

Ideally, the aim is to demonstrate that any proposed CR proxy (sociocultural or functional brain measure) moderates the relationship between an indicator of brain abnormality/pathology and clinical/cognitive status. That is, cognitive performance should be predicted by the interaction between that proposed factor and brain/pathology status.

A simple correlation of cognitive test performance with a sociobehavioral proxy of CR is not sufficient to establish that the test performance reflects CR because it proves no insight into how that influences the relationship between the brain and clinical or cognitive performance outcome.

In some situations, perhaps for hypothesis generation, it may be sufficient to demonstrate that a hypothesized CR proxy or measure is associated with cognitive performance after partialing out the effects of brain change, pathology, or insult. For example, in a multiple regression analysis predicting cognition that includes brain atrophy/pathology measures and a hypothesized CR proxy, the proxy should account

for additional predictive variance. In this analysis, the new CR proxy simply adds predictive information (a protective factor), a weaker form of CR evidence than moderation.

From a neurobiological point of view, CR remains a black box. Research spanning human and animal models will be required to elucidate CR at that level.

5.1.1. Example 1: A longitudinal study of the differential risk of incident AD in people with higher or lower education

Here, the presence of comparable amounts of AD pathology across educational groups is implicitly assumed. The outcome is meeting the clinical diagnostic criteria for AD at follow-up. Because education is known to be associated with higher premorbid scores on many formal psychometric measures, appropriate statistical methods must be used to address the question of whether the diagnosis of AD is not itself confounded with education, the proxy thought to reflect CR. The underlying logic is that given equal underlying AD-related brain changes, individuals with greater educational exposure are less likely to become demented. For an exposure to be considered as enhancing CR, it should be associated with reduced incidence of a definitive clinical outcome (such as the clinical expression of AD) given equivalent level of neuropathology.

In epidemiological studies, risk factors for dementia are sometimes used in the absence of brain measures. Although completely uninformative of brain processes or pathology, these models can test if individuals with higher levels of CR proxies can tolerate higher risk factor levels.

5.1.2. Example 2: A cross-sectional study examining the clinical severity of AD

An appropriate standard of research would be to demonstrate that a putative protective factor or brain feature moderates the relationship between underlying AD-related brain changes and a clinical variable such as cognition or day-to-day function. For example, one could explore whether education moderates the relationship between clinical dementia severity and disease pathology, the latter quantified in terms of amyloid/tau burden or patterns of neurodegeneration, atrophy, hypometabolism, etc. It should be noted that, although education may be identified as a moderator, in most situations, it would be inappropriate to assume causality. Therefore, cognitive or neural mechanism that might underlie this effect still needs to be investigated with a longitudinal or intervention design.

5.1.3. Example 3: Longitudinal design incorporating measures of brain and clinical change

For example, one could explore whether some life exposure conceptually linked to CR moderates the relationship between change in brain status (e.g., volume, white matter tract integrity, white matter hyperintensity burden) and change in cognition. One might expect that in individuals with higher versus lower CR, the relationship between brain status and cognition is weaker because higher CR means greater ability to adapt and therefore cognition will be less susceptible to change in brain state.

5.1.4. Example 4: Functional imaging approaches to studying CR

Various functional imaging approaches have been used to try to quantify, better understand, or capture the "neural implementation" of CR. It is important to consider the possibility that the neural implementation of CR might differ as a function of different CR proxies and their related life exposures.

One goal is to identify a functional network, either resting or task-related, whose expression moderates the relationship of brain status (e.g., volume, white matter tract integrity, amyloid burden) to cognition. Optimally the expression of that network also correlates with a typical CR sociobehavioral proxy. Such a network may help both measure CR and elucidate its neural substrate.

Other approaches can also elucidate the neural implementation of CR. Often a distinction is made between networks that preexist age-related brain changes or pathology and those that emerge in response to these changes.

For preexisting networks, the supposition is that there is natural interindividual variability in the brain networks that underlie the performance of any task. This interindividual variability could be influenced by CR-related exposures and thus help represent the neural implementation of CR. Interindividual variability could be in the form of differing efficiency or capacity of functional brain networks, or in greater flexibility in the networks that can be invoked to perform a task. Although healthy individuals may invoke these networks in response to day-to-day cognitive challenges, the networks could also help an individual cope with brain changes: an individual whose networks are more efficient, have greater capacity, or are more flexible might be more capable of coping with the disruption imposed by brain pathology.

Efficiency can be defined as the degree to which a given task-related brain network must become activated to accomplish a given task. A more efficient network will show less activation to produce the same (or better) level of performance. Thus, an individual with greater efficiency will show less task-related activation at a given level of task demand. *Capacity* can be defined as the maximum degree to which a task-related brain network can be activated to keep performing a task in the face of increasing demands. Again, this maximum capacity varies across individuals. Higher CR might be associated with either greater efficiency or capacity. The behavioral implication of flexibility is that an individual with higher CR may have more varied solution strategies available. This might be reflected by the ability to utilize alternate networks during task performance that result in more successful performance. Functional magnetic resonance imaging studies of this concept would require careful application of these ideas to specific brain areas or networks that are consistent with solution strategies for a specific task.

With regard to networks that emerge in response to brain aging or pathology, the concept of *compensation* is often invoked. In response to these brain changes, individuals may recruit brain structures or networks (and thus cognitive strategies) not normally used by individuals with "intact" brains. Compensation can result in improved performance. Alternately it could result in maintenance of performance, but perhaps at a lower level then when compensation is not required. Given a specific level of BR and brain pathology, there are several possibilities. Higher CR could be associated with the lack compensation (while compensation is seen at lower levels of CR). Alternately, individuals with higher CR may compensate more successfully to maintain function, albeit at a lower level.

5.2. Brain reserve

Brain reserve can be studied cross-sectionally, looking for new links between structural brain features and variability in cognitive status with age, disease, or brain injury. In cross-sectional studies, intracranial volume does not change as a consequence of pathology, so it could be considered as a practical, convenient proxy of premorbid brain structure/size.

A goal of longitudinal studies could be to demonstrate that a higher degree of some brain features (e.g., regional volume, cortical surface area, patterns of cortical thickness, white matter microstructural properties), measured before the putative age- or pathology-related brain changes, is associated with lower subsequent risk of reaching a clinical outcome or of cognitive decline.

In animal studies, these questions might be addressed directly, so that BR concepts might be developed that encompass all scales from molecular to cellular to systems. In such an experimental context, bridging to CR-like concepts might become possible.

5.3. Brain maintenance

For BM, the goal is to demonstrate that a certain genetic background or life exposure results in a healthier brain outcome, for example, less rapid volume loss, less accumulation of microvascular brain changes, less amyloid accumulation or tau burden.

In the study of brain morphological features (for instance, cortical thickness or brain volume), BR and BM cannot be discriminated in cross-sectional designs. For instance, where higher thickness is desirable, BR would postulate that those with high reserve have thicker brains, whereas BM would postulate that maintainers experience less loss of thickness. Thus, in this case, a single time point measurement cannot separate high BR individuals from maintainers. Making this distinction is complex but can be aided by a longitudinal design.

Where BM-related life exposures intersect with CR or BR variables, there is considerable scope for these research areas to enrich each other. A form of BM is also higher resistance to the progression of primary pathology itself. Thus, a general approach to assess BM would be to examine longitudinally if individuals vary in how much age- or disease-related brain anomalies they accumulate over time and assess which factors (e.g., genetic, lifestyle, neural) are associated with different trajectories.

As in the case of BR, experimental neurobiological basic research of BM and CR could generate mechanistic insights that would aid the integration across the scales and domains. Hard to define yet critical concepts such as "plasticity" at the synaptic, cellular, and functional level as the fundamental mechanistic basis of the relationship between structure and function and their inherent mechanistic complexity would need to be related to the ideas embodied in the constructs of CR, BR, and BM to increase explanatory and predictive power.

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RESEARCH IN CONTEXT

1. Systematic review: ■■■.
2. Interpretation: ■■■.
3. Future directions: ■■■.